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Studies on Pyrimidine Derivatives. XXVIII.[1] Synthesis of Pyridopyrimidine Derivatives by Cross-coupling of Halopyrimidines with Olefins and Acetylenes

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Three kinds of pyridopyrimidines were synthesized from appropriate pyrimidine derivatives. Cross-coupling of 4-amino-5-iodopyrimidines with α,β-unsaturated carboxylic esters followed by ring-closure afforded pyrido[2,3-*d*]pyrimidines.

Ammonolysis of 4-ethoxycarbonyl-5-phenylethynyl- and 5-ethoxycarbonyl-4-phenylethynyl-pyrimidines which were obtained by cross-coupling of the corresponding halopyrimidines with phenylacetylene, gave pyrido[3,4-*d*]- and pyrido[4,3-*d*]-pyrimidines, respectively.

Keywords——palladium-catalyzed cross-coupling reaction; ring-closure reaction; 5-iodopyrimidine; phenylethynylpyrimidine; styrylpyrimidine; ethyl 5-pyrimidineacrylate; pyridopyrimidine

The development of practical methods for the synthesis of various pyridopyrimidines, in view of their structural relation to pteridine, is of interest in the field of medicinal chemistry. Although there are several papers dealing with the synthesis of pyridopyrimidines, most work has been concentrated on the ring-closure reaction of pyridine derivatives having appropriate substituents.[2] The synthesis of such fused ring systems from pyrimidine derivatives has not been well explored, presumably due to the poor availability of suitable pyrimidine derivatives as starting materials.

The present paper describes the synthesis of three kinds of pyridopyrimidines by the ring-closure of ethynyl- and ethenyl-pyrimidines, which were prepared by the palladium catalyzed cross-coupling of halopyrimidines with acetylenic and ethylenic compounds.

2,6-Dimethyl-5-iodo-4(3*H*)-pyrimidinone (**1b**), prepared by the iodination[3] of 2,6-dimethyl-4(3*H*)-pyrimidinone, was easily converted to 4-chloro-2,6-dimethyl-5-iodopyrimidine (**2b**) by treatment with phosphoryl chloride under reflux. When **2b** was heated at 120°C in a sealed tube with ethanolic ammonia, 4-amino-2,6-dimethyl-5-iodopyrimidine (**3b**) was obtained in 85% yield. Since many 5-iodo-alkylpyrimidines were reported[4] to couple with ethyl acrylate in the presence of palladium(II) acetate in triethylamine, **3b** was treated with ethyl acrylate under various cross-coupling conditions. When palladium(II) chloride was used in the absence of triphenylphosphine, good results were obtained, and ethyl 4-amino-2,6-dimethyl-5-pyrimidineacrylate (**4b**) was isolated as colorless needles. The subsequent ring-closure reaction of **4b** under basic conditions readily afforded 7,8-dihydro-2,4-dimethyl-7-oxopyrido[2,3-*d*] pyrimidine (**5b**) in satisfactory yield, although a *trans* configuration was assigned to the olefinic side chain of **4b** on the basis of its proton magnetic resonance (PMR) spectrum. The overall yield of **5b** from **1b** was 48%.

When **2b** was heated with ethyl acrylate in triethylamine in the presence of a catalytic amount of palladium(II) acetate, cross-coupling occurred at the 5-position, and ethyl 4-chloro-2,6-dimethyl-5-pyrimidineacrylate (**8**) was obtained as a sole product. The 5-pyrimidineacrylate (**8**) was alternatively synthesized from **1b**. Namely, the cross-coupling of **1b** with ethyl acrylate under similar conditions gave ethyl 3,4-dihydro-2,6-dimethyl-4-oxo-5-pyrimidineacrylate (**9**), which was smoothly transformed into **8** by treatment with phosphoryl chloride in the usual fashion. The ammonolysis of **8** with ethanolic ammonia at 120°C in a sealed tube gave rise to the ring-closure product (**5b**) in good yield.

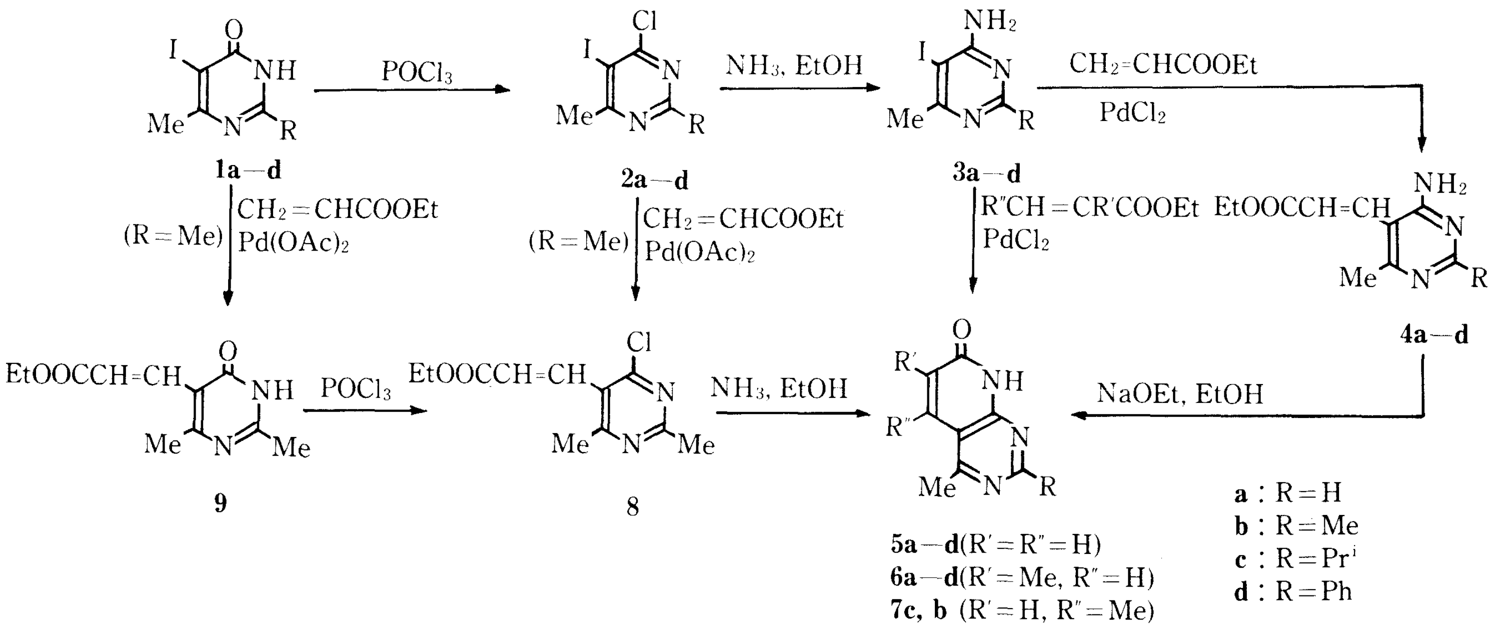

Chart 1

TABLE I. Spectral Data for Ethyl *trans*-4-Amino-6-methyl-5-pyrimidineacrylates (**4a**—**d**)

No.	IR ($CHCl_3$) cm^{-1}		PMR ($CDCl_3$) δ		
	$-NH_2$	>C=O	H>C=C<H	$-NH_2$	Other protons
4a	3520, 3400	1720	6.32 (1H, d, *J*=17.0 Hz), 7.70 (1H, d, *J*=17.0 Hz)	5.70 (2H, s)	1.35 (3H, t, *J*=7.0 Hz), 2.45 (3H, s), 4.29 (2H, q, *J*=7.0 Hz), 8.39 (1H, s)
4b	3520, 3410	1720	6.30 (1H, d, *J*=17.0 Hz), 7.70 (1H, d, *J*=17.0 Hz)	5.65 (2H, s)	1.31 (3H, t, *J*=7.0 Hz), 2.45 (6H, s), 4.25 (2H, q, *J*=7.0 Hz)
4c	3540, 3420	1720	6.28 (1H, d, *J*=17.0 Hz), 7.77 (1H, d, *J*=17.0 Hz)	5.25 (2H, s)	1.28 (6H, d, *J*=7.0 Hz), 1.31 (3H, t, *J*=7.0 Hz), 2.42 (3H, s), 2.20—3.20 (1H, m), 4.29 (2H, q, *J*=7.0 Hz)
4d	3530, 3410	1720	6.30 (1H, d, *J*=17.0 Hz), 7.72 (1H, d, *J*=17.0 Hz)	5.29 (2H, s)	1.31 (3H, t, *J*=7.0 Hz), 2.50 (3H, s), 4.25 (2H, q, *J*=7.0 Hz), 7.40—7.55 (3H, m), 8.10—8.60 (2H, m)

On the basis of the total yield and experimental simplicity, the above three methods seem to be equally useful for the preparation of the final product.

In addition to the above synthesis, the cross-coupling reactions of **3a**—**d** with ethyl methacrylate and with ethyl crotonate were carried out. In the former case, 7,8-dihydro-7-oxopyrido[2,3-*d*]pyrimidines (**6a**—**d**) were directly obtained, instead of the expected intermdiates (**4a**—**d**). The reaction of **3a**, **b** with ethyl crotonate failed to give any significant products, but **7c** and **7d** were directly obtained in moderate yields by the reaction of **3c** and **3d** with ethyl crotonate, respectively.

The construction of pyrido[3,4-*d*]pyrimidine and pyrido[4,3-*d*]pyrimidine ring systems was investigated by the cross-coupling of phenylacetylene with halopyrimidines containing an ethoxycarbonyl group in the neighborhood of the coupling position. Namely, when ethyl 5-bromo-2-methyl-4-pyrimidinecarboxylate (**10**) was heated with phenylacetylene in the presence of bis(triphenylphosphine)palladium(II) chloride and cuprous iodide in triethylamine for 24 h, ethyl 2-methyl-5-phenylethynyl-4-pyrimidinecarboxylate (**11**) was isolated as a colorless liquid.

TABLE II. Ethyl *trans*-4-Amino-6-methyl-5-pyrimidineacrylates (**4a**—**d**)

No.	Yield (%)	mp (°C)	Appearance (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N
4a	72	161—162	Prisms (Acetone)	$C_{10}H_{13}N_3O_2$	57.96 (58.04	6.32 6.13	20.28 20.48)
4b	81	151—152	Needles (Acetone)	$C_{11}H_{15}N_3O_2$	59.71 (59.73	6.83 6.61	18.99 18.89)
4c	65	92—93	Needles (Hexane)	$C_{13}H_{19}N_3O_2$	62.62 (62.33	7.68 7.77	16.86 16.59)
4d	71	121—122	Needles (Ether–hexane)	$C_{16}H_{17}N_3O_2$	67.82 (68.07	6.05 6.10	14.83 14.97

TABLE III. Spectral Data for Pyrido[2,3-*d*]pyrimidines (**5a**—**d**, **6a**—**d**, and **7c**, **d**)

No.	IR ($CHCl_3$) cm^{-1}		PMR δ			
	>NH	>C=O	Solvent	Ring protons	>NH	Other protons
5a	3380	1680	CF_3COOH	6.71 (1H, d, $J=12.0$ Hz) 7.85 (1H, d, $J=12.0$ Hz) 9.26 (1H, s)	—	3.23 (3H, s)
5b	3370	1680	CF_3COOH	6.70 (1H, d, $J=12.0$ Hz) 7.85 (1H, d, $J=12.0$ Hz)	—	3.00 (3H, s), 3.10 (3H, s)
5c	3370	1680	$CDCl_3$	6.72 (1H, d, $J=12.0$ Hz) 7.93 (1H, d, $J=12.0$ Hz)	11.30 (1H, s)	1.34 (6H, d, $J=7.0$ Hz) 2.73 (3H, s), 2.90—3.60 (1H, m)
5d	3370	1670	CF_3COOH	6.70 (1H, d, $J=12.0$ Hz) 7.88 (1H, d, $J=12.0$ Hz)	—	2.50 (3H, s), 7.65—8.70 (5H, m)
6a	3370	1670	CF_3COOH	7.70 (1H, s), 9.30 (1H, s)	—	3.12 (3H, s), 3.30 (3H, s)
6b	3370	1680	$CDCl_3$	7.75 (1H, s)	11.60 (1H, s)	2.30 (3H, s), 2.71 (3H, s) 2.80 (3H, s)
6c	3380	1670	$CDCl_3$	7.77 (1H, s)	10.70 (1H, s)	1.33 (6H, d, $J=7.0$ Hz), 2.32 (3H, s), 2.72 (3H, s), 3.10—3.60 (1H, m)
6d	3370	1670	CF_3COOH	7.60 (1H, s)	—	2.47 (3H, s), 3.20 (3H, s), 7.65—8.65 (5H, m)
7c	3380	1680	$CDCl_3$	6.52 (1H, s)	10.90 (1H, s)	1.34 (6H, d, $J=7.0$ Hz), 2.65 (3H, s), 2.90—3.60 (1H, m)
7d	3380	1680	CF_3COOH	6.50 (1H, s)	—	2.45 (3H, s), 2.70 (3H, s), 7.50—8.50 (5H, m)

Table IV. Pyrido[2,3-*d*]pyrimidines(**5a**—**d**, **6a**—**d**, and **7c**, **d**) from **3a**—**d** and **4a**—**d**

No.	Yield (%)	mp (°C)	Appearance (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N
5a	85	265—270	Prisms (Acetone)	$C_8H_7N_3O$	59.62 (59.46	4.38 4.31	26.07 26.03)
5b	82	221—222	Needles (Acetone)	$C_9H_9N_3O$	61.70 (61.43	5.18 5.03	23.99 23.85)
5c	80	136—137	Prisms (Hexane)	$C_{11}H_{13}N_3O$	65.00 (65.18	6.43 6.45	20.68 20.60)
5d	85	240—241	Prisms (Benzene)	$C_{14}H_{11}N_3O$	70.87 (70.67	4.67 4.49	17.71 17.67)
6a	62	142—143	Needles (Ether-hexane)	$C_9H_9N_3O$	61.70 (61.65	5.18 5.32	23.99 24.03)
6b	65	144—145	Needles (Benzene)	$C_{10}H_{11}N_3O$	63.48 (63.52	5.86 5.79	22.21 21.98)
6c	70	138—139	Needles (Ether)	$C_{12}H_{15}N_3O$	66.34 (66.45	6.96 7.13	19.34 19.45)
6d	53	239—240	Needles (Ether)	$C_{15}H_{13}N_3O$	71.60 (71.69	5.32 5.21	16.58 16.72)
7c	40	180—181	Scales (Cyclohexane)	$C_{12}H_{15}N_3O$	66.34 (66.15	6.96 7.02	19.34 19.44)
7d	50	265—270 (dec.)	Needles (Acetone)	$C_{15}H_{13}N_3O$	71.69 (71.81	5.21 5.23	16.72 16.98)

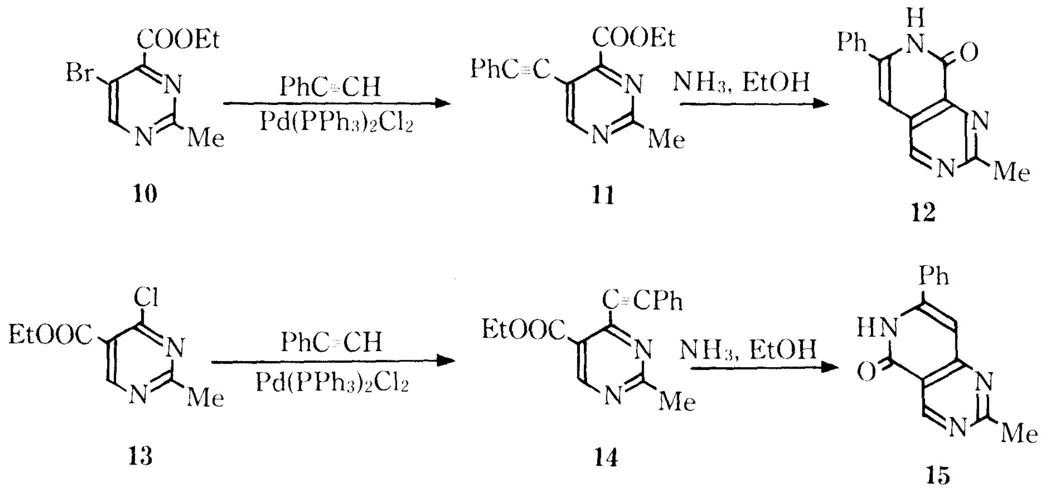

Chart 2

Ethyl 4-chloro-2-methyl-5-pyrimidinecarboxylate (**13**) reacted smoothly with phenylacetylene under the same catalytic conditions at room temperature, and ethyl 2-methyl-4-phenylethynyl-5-pyrimidinecarboxylate (**14**) was obtained in good yield. In general, the cross-coupling of 4-chloropyrimidines with terminal acetylenes is known to proceed under reflux.[1] In the case of **13**, the electron-withdrawing effect of the neighboring ethoxycarbonyl group may facilitate the reaction. The pyrmidinecarboxylic esters (**11** and **14**) thus obtained readily cyclized to give 7,8-dihydro-2-methyl-8-oxo-6-phenylpyrido[3,4-*d*]pyrimidine (**12**) and 5,6-dihydro-2-methyl-5-oxo-7-phenylpyrido[4,3-*d*]pyrimidine (**15**), respectively, on heating with ethanolic ammonia.

Two reaction pathways can be considered for the above cyclization. One is the intramolecular addition of a carbamoyl group formed from an ester group to the carbon-carbon triple bond, and the other is the condensation of an enamine moiety formed from an acetylenic bond with the neighboring ethoxycarbonyl group. In our previous investigation,[5] methyl

Table V. 4-Chloro-5-iodopyrimidines (**2a**, **b**, **d**)

No.	Yield (%)	mp (°C) [bp(mmHg)]	PMR($CDCl_3$) δ	Formula	Analysis (%) Calcd (Found)		
					C	H	N
2a	75	117—118	2.70 (3H, s) 8.72 (1H, s)	$C_5H_4ClIN_2$	23.60 (23.52	1.58 1.59	11.01 10.55)
2b	80	92—94 [131—132(14)]	2.55 (3H, s) 2.70 (3H, s)	$C_6H_6ClIN_2$	26.84 (26.91	2.25 2.31	10.43 10.37)
2d	83	101—102	2.80 (3H, s) 7.30—7.70 (3H, m) 8.30—8.60 (2H, m)	$C_{11}H_8ClIN_2$	40.07 (40.15	2.44 2.52	8.49 8.33)

Table VI. 4-Amino-5-iodopyrimidines (**3a**—**d**)

No.	Yield (%)	mp (°C) (Recrystn. solvent)	IR (cm^{-1}) ($CHCl_3$) $-NH_2$	PMR ($CDCl_3$) δ		Formula	Analysis (%) Calcd (Found)		
				$-NH_2$	Other protons		C	H	N
3a	80	164—165.5 (MeOH)	3540 3410	5.65 (2H, s)	2.60 (3H, s) 8.33 (1H, s)	$C_5H_5IN_3$	25.55 (25.64	2.57 2.43	17.88 17.52)
3b	85	141—142[7] (Ether)	3540 3410	5.51 (2H, s)	2.50 (3H, s) 2.62 (3H, s)				
3c	95	145—147 (Hexane)	3510 3400	5.45 (2H, s)	1.37 (6H, d, J=7.0 Hz) 2.56 (3H, s) 2.70—3.30 (1H, m)	$C_8H_{12}IN_3$	34.65 (34.91	4.33 4.36	15.16 15.04)
3d	85	166—167 ($CHCl_3$)	3530 3410	—[a]	2.90 (3H, s) 7.40—8.30 (5H, m)	$C_{11}H_{10}IN_3$	42.47 (42.62	3.24 3.37	13.51 13.78)

a) In CF_3COOH.

4-pyrimidinecarboxylates reacted with ammonia at room temperature, whereas the reaction of ethynylpyrimidines with amines gave the enamines slowly. Accordingly, the intramolecular addition is concluded to the more likely pathway.

Experimental

All melting points and boiling points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. PMR spectra were taken at 60 MHz with a JEOL JNM-PMX 60 spectrometer. Chemical shifts are expressed in δ value. The following abbreviations are used: s=singlet, d=doublet, q=quartet, and m=multiplet.

4-Chloro-5-iodo-6-methylpyrimidines (**2a**, **b**, **d**)——A mixture of 5-iodo-6-methyl-4(3*H*)-pyrimidinones (**1a**, **b**, **d**) (0.01 mol) and $POCl_3$ (10 ml) was refluxed for 1—2 h. After removal of excess $POCl_3$, the residue was poured into ice-water. The mixture was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by distillation under reduced pressure or by recrystallization for **2a** (from ether) and **2b**, **d** (from hexane).

4-Chloro-5-iodo-2-isopropyl-6-methylpyrimidine (**2c**) was prepared according to the literature.[6]

4-Amino-5-iodo-6-methylpyrimidines (**3a**—**d**)——An EtOH solution (10 ml) of **2a**—**d** was saturated with NH_3 gas, and the mixture was heated at 120°C in a sealed tube for 12 h. After removal of the EtOH, the residue was diluted with H_2O. The resulting mixture was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was recrystallized from the solvent shown in Table VI.

Ethyl *trans*-4-Amino-6-methyl-5-pyrimidineacrylate (**4a**—**d**)——A mixture of **3a**—**d** (5 mmol), ethyl acrylate (6 mmol), $PdCl_2$ (30 mg), Et_3N (6 mmol), and MeCN (2 ml) was heated at 120°C in a sealed tube for 24 h. After removal of the MeCN, the residue was diluted with H_2O. The mixture was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extracts were purified by SiO_2 column chromatography with C_6H_6: AcOEt (9: 1) for **4a**—**c** and $CHCl_3$ for **4d**. Recrystallization from the solvent shown in Table II gave colorless crystals.

Ethyl *trans*-3,4-Dihydro-2,6-dimethyl-4-oxo-5-pyrimidineacrylate (9)——A mixture of **1b** (2.5 g, 0.01 mol), ethyl acrylate (1.2 g, 0.012 mol), $Pd(OAc)_2$ (60 mg), and Et_3N (5 ml) was heated at 120°C in a sealed tube for 24 h. After removal of the Et_3N, the residue was diluted with H_2O. The mixture was made alkaline with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by Al_2O_3 column chromatography using $CHCl_3$ as an eluent. Recrystallization from AcOEt gave colorless needles, mp 222—223°C. Yield 1.3 g (60%). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1715, 1670. PMR ($CDCl_3$): 1.33 (3H, t, $J=7.0$ Hz), 2.53 (6H, s), 4.23 (2H, q, $J=7.0$ Hz), 7.17 (1H, d, $J=17.0$ Hz), 7.66 (1H, d, $J=17.0$ Hz), 12.93—14.35 (1H, broad). *Anal.* Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.47; H, 6.36; N, 12.60.

Ethyl *trans*-4-Chloro-2,6-dimethyl-5-pyrimidineacrylate (8)——i) A mixture of **9** (1.1 g, 0.005 mol) and $POCl_3$ (10 ml) was refluxed for 1.5 h. The mixture was concentrated under reduced pressure and the residue was poured into ice-water. The resulting mixture was made alkaline with K_2CO_3 and then extracted with $CHCl_3$. The $CHCl_3$ extract was distilled under reduced pressure to give a colorless liquid, bp 122—125°C (2 mmHg). Yield 1.0 g (83%).

ii) A mixture of **2b** (1.35 g, 0.005 mol), ethyl acrylate (0.6 g, 0.006 mol), $Pd(OAc)_2$ (30 mg), and Et_3N (3 ml) was heated at 120°C in a sealed tube for 24 h. After removal of the Et_3N, the residue was diluted with H_2O. The mixture was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by SiO_2 column chromatography using C_6H_6 as an eluent. Distillation under reduced pressure gave a colorless liquid, bp 122—125°C (2 mmHg). Yield 0.6 g (50%). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1710. PMR ($CDCl_3$): 1.34 (3H, t, $J=7.0$ Hz), 2.60 (3H, s), 2.66 (3H, s), 4.33 (2H, q, $J=7.0$ Hz), 6.40 (1H, d, $J=17.0$ Hz), 7.75 (1H, d, $J=17.0$ Hz). *Anal.* Calcd for $C_{11}H_{13}ClN_2O_2$: C, 54.89; H, 5.44; Cl, 14.73; N, 11.64. Found: C, 55.02; H, 5.42; Cl, 14.60; N, 11.59.

7,8-Dihydro-4-methyl-7-oxopyrido[2,3-*d*]pyrimidine (5a—d) from 4a—d——An abs. EtOH–EtONa solution (30 ml; Na, 0.46 g, 0.02 g atom) of **4a**—**d** (0.005 mol) was refluxed for 1 h. After removal of the EtOH, the residue was diluted with H_2O, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was recrystallized from the solvents shown in Table IV to give colorless crystals.

7,8-Dihydro-2,4-dimethyl-7-oxopyrido[2,3-*d*]pyrimidine (5b) from 8——An EtOH solution (10 ml) of **8** (1.2 g, 0.005 mol) was saturated with NH_3 gas, and the mixture was heated at 120°C in a sealed tube for 12h. After removal of the EtOH, the residue was washed with H_2O and recrystallized from acetone to give colorless needles, mp 221—222°C. Yield 0.67 g (75%).

7,8-Dihydro-4,6(5)-dimethyl-7-oxopyrido[2,3-*d*]pyrimidines (6a—d and 7c, d) from 3a—d——A mixture of **3a**—**d** (0.005 mol), ethyl methacrylate (or crotonate) (0.006 mol), $PdCl_2$ (30 mg), Et_3N (0.006 mol), and MeCN (2 ml) was heated at 120°C in a sealed tube for 24 h. After removal of the solvent, the residue was diluted with H_2O. The mixture was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extracts were purified by SiO_2 column chromatography using C_6H_6: AcOEt (9: 1) as an eluent. Recrystallization from the solvents shown in Table IV gave colorless crystals.

Ethyl 2-Methyl-5-phenylethynyl-4-pyrimidinecarboxylate (11)——A mixture of ethyl 5-bromo-2-methyl-4-pyrimidinecarboxylate (**10**) (2.45 g, 0.01 mol), phenylacetylene (1.2 g, 0.012 mol), $Pd(PPh_3)_2Cl_2$ (160 mg), CuI (80 mg), and Et_3N (10 ml) was refluxed for 24 h. After removal of the Et_3N, the residue was diluted with H_2O. The mixture was made alkaline with K_2CO_3 and then extracted with $CHCl_3$. The $CHCl_3$ extract was purified by SiO_2 column chromatography using hexane as an eluent. Distillation under reduced pressure gave a colorless liquid, bp 160—165°C (3 mmHg). Yield 1.6 g (60%). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 2250, 1730. PMR ($CDCl_3$): 1.45 (3H, t, $J=7.0$ Hz), 2.84 (3H, s), 4.50 (2H, q, $J=7.0$ Hz), 7.20—7.85 (5H, m), 8.90 (1H, s). *Anal.* Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.31; H, 5.25; N,10.49.

7,8-Dihydro-2-methyl-8-oxo-6-phenylpyrido[3,4-*d*]pyrimidine (12)——An EtOH solution (5 ml) of **11** (1.3 g, 0.005 mol) was saturated with NH_3 gas, and the mixture was heated at 120°C in a sealed tube for 12 h. After removal of the solvent, the residue was recrystallized from MeOH to give colorless needles, mp 190—191°C. Yield 1.0 g (90%). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3400, 1705. PMR ($CDCl_3$): 2.80 (3H, s), 5.50—6.30 (1H, broad), 7.25—8.00 (6H, m), 8.96 (1H, s). *Anal.* Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.70; H, 4.80; N, 17.65.

Ethyl 2-Methyl-4-phenylethynyl-5-pyrimidinecarboxylate (14)——A mixture of ethyl 4-chloro-2-methyl-5-pyrimidinecarboxylate (**13**) (2.0 g, 0.001 mol), phenylacetylene (1.2 g, 0.012 mol), $Pd(PPh_3)_2Cl_2$ (160 mg), CuI (80 mg), and Et_3N (10 ml) was stirred at room temperature for 24 h. After removal of the solvent, the residue was diluted with H_2O. The mixture was made alkaline with K_2CO_3 and then extracted with $CHCl_3$. The $CHCl_3$ extract was purified by SiO_2 column chromatography using hexane as an eluent. Recrystallization from hexane gave colorless needles, mp 89—90°C. Yield 2.0 g (75%). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 2245, 1705. PMR ($CDCl_3$): 1.41 (3H, t, $J=7.0$ Hz), 2.70 (3H, s), 4.37 (2H, q, $J=7.0$ Hz), 7.20—7.90 (5H, m), 9.20 (1H, s). *Anal.* Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.40; H, 5.31; N, 10.29.

5,6-Dihydro-2-methyl-5-oxo-7-phenylpyrido[4,3-*d*]pyrimidine (15)——An EtOH solution (5 ml) of **14** (1.3 g, 0.005 mol) was saturated with NH_3 gas, and the mixture was heated at 120°C in a sealed tube for 12 h. After removal of the solvent, the residue was recrystallized from EtOH to give colorless needles, mp 279—283 °C. Yield 1.1 g (95%). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3380, 1660. PMR ($CDCl_3$): 3.13 (3H, s), 7.49 (1H, s), 7.50—8.20

(5H, m), 9.10 (1H, s). *Anal.* Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.79; H, 4.60; N, 17.77.

References and Notes

1) Part XXVII: K. Tanji, T. Sakamoto, and H. Yamanaka, *Chem. Pharm. Bull.*, **30**, 1865 (1982).
2) W.J. Irwin and D.G. Wibberley, "Advances in Heterocyclic Chemistry," Vol. 10, ed. by A.R. Katritzky and A.J. Boulton, Academic Press Inc., New York, 1969, pp. 149—198.
3) The iodination of 2- and 4-pyrimidinones is not generally well known, though the chlorination and bromination of such compound are relatively commonly used. The results of the iodination carried out during the present investigation will be reported in the following paper.
4) K. Edo, T. Sakamoto, and H. Yamanaka, *Chem. Pharm. Bull.*, **27**, 193 (1979).
5) T. Sakamoto, T. Sakasai, and H. Yamanaka, *Chem. Pharm. Bull.*, **28**, 571 (1980).
6) K. Edo, T. Sakamoto, and H. Yamanaka, *Chem. Pharm. Bull.*, **26**, 3843 (1978).
7) O.O. Orazi, R.A. Corral, and H.E Bertorello, *J. Org. Chem.*, **30**, 1101 (1965).